PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	09-02-2006
Applicant's or agent's file reference MH/LB 54797	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2005/001336	14-09-2005	14-09-2004

International Patent Classification (IPC) or both national classification and IPC
See Supplemental Box

Applicant
AGVALD, Per et al

1. This opinion contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☒ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

   If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

   If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

   For further opinions, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Form PCT/ISA/237 (cover sheet) (April 2005)

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Cover sheet

INTERNATIONAL PATENT CLASSIFICATION (IPC):

A61K 33/00 (2006.01)
A61K 47/10 (2006.01)
A61K 47/26 (2006.01)
A61K 47/36 (2006.01)
A61K 47/42 (2006.01)
A61P 11/00 (2006.01)
A61K 9/107 (2006.01)

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☒ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The scope of the claims in the present application is considerable wider than the scope of application SE040222-6. The claims relate to a number of compositions comprising compounds not mentioned in application SE040222-6.

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. See specification below

because:

☒ the said international application, or the said claims Nos. 29-34, 39-40
relate to the following subject matter which does not require an international search *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. X
are so unclear that no meaningful opinion could be formed *(specify)*:

X Claims 1-3, 8, 13-14, 16, 18, 20, 22, 26, 35-36 partly claims 10-11, 27-28, 37-38. Present claims 1, 26 and partly claims 27-28 relate to a composition and claims 35-36 and

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☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box III.2

partly 38 to a method defined by reference to a desirable characteristic or property, namely that it comprises a compound capable of forming a reversible bond or association with NO. The claims cover all compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of such compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lacks clarity (Article 6 PCT). An attempt is made to define the composition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compositions comprising the compounds, or compounds from well defined groups, mentioned in claims 4-25. A search has also been carried out for general terms, such as alcohols, sugars and proteins, and all compounds in table 1 in the description.

In present claims 2-3 and partly claims 27-28 and 37-38 the compound capable of forming a reversible bond or association with NO is specified to a carbohydrate or a compound comprising at least one hydroxyl group. However, the specifications are vague and unclear. The claims relate to an extremely large number of possible compositions. In fact, the claims contain so many options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. The same is true for claims 8, 13-14, 16, 18, 20, 22 and partly for claims 10-11 (the terms higher carbohydrate polymer and higher polysaccharide) where wide and vague specifications are used.

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Consequently, the search has been carried out for those parts of the application which appear to be clear and concise, namely those parts relating to compositions comprising the compounds, or compounds from well-defined groups, mentioned in claims 4-25. A search has also been carried out for general terms, such as sugars, alcohols and proteins, and all compounds in table 1 in the description.

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☒ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not Complied with for the following reasons:

The following separate inventions were identified:

1: Claims 4-12 and partly claims 1-3, 15, 26-40 directed to compositions comprising sugars.

2: Claims 13-14, 16-21 and partly claims 1-3, 15, 26-40 directed to compositions comprising alcohols.

3: Claims 22-25 and partly claims 1-2, 26-40 directed to compositions comprising proteins and amino acids.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☒ all parts

   ☐ the parts relating to claims Nos. _____

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	4-12, 14-21, 26, 28, 35-38	YES
	Claims	1-3, 13, 22-25, 27	NO
Inventive step (IS)	Claims	4-9, 12, 15, 17, 19, 21	YES
	Claims	1-3,10-11,13-14,16,18,20,22-	NO
Industrial applicability (IA)	Claims	1-28, 35-38	YES
	Claims		NO

2. Citations and explanations:

The invention relates to compositions comprising compounds, preferably carbohydrates, capable of forming a reversible bond or association with nitric oxide (NO). Formulations and methods for use in the delivery to a mammal are also disclosed.

Reference is made to the following documents:
D1: US2002061879 A1
D2: US6417162 B1
D3: US2003050305 A1
D4: WO0057891 A1
D5: WO9638136 A1
D6: US6352709 B1
D7: WO9635416 A1
D8: US2004162243 A1
D9: EP1023900 A2
D10: WO9422482 A1

Documents D1-D2 describe compositions comprising nitric oxide (NO) donors. In both documents it is shown that sugars, proteins and alcohols can be associated with NO. Among the compounds that are described are ON-C-sugars, ON-O-sugars, ON-N-sugars, O-nitrosoalcohols, S-nitroso-N-acetylcysteine and S-nitroso-polypeptides. It is stated that the reactive form of nitric oxide can be provided by gaseous nitric oxide. Further, in both documents it is explained that the compositions can be formulated for parenteral administration.

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Documents D3-D8 describe different compositions and medical devices comprising nitric oxide donors. The documents that relate to medical devices (D5-D7) describe localized use of nitric oxide donors to prevent internal tissue damage. In all the documents it is shown that sugars and polypeptides can be associated with NO. Among the compounds that are described are ON-C-sugars, S-nitrosylated-sugars, S-nitroso-N-acetylcysteine, S-nitroso-polypeptides, S-nitroso-cysteine, polynitrosylated albumin and S-nitrosalbumin. In all the documents it is stated that the reactive form of nitric oxide can be provided by gaseous nitric oxide. D5-D7 explain that nitrosation can be achieved by exposure to NO gas under anaerobic conditions. Further, in all documents it is explained that the compositions can be formulated for parenteral administration. In all the documents emulsions are described as suitable vehicles for parenteral administration.

Document D9 describes compositions containing S-nitroso-lipoproteins. The invention relates to nitrosylation of proteins and amino acids as therapeutic modality. S-nitroso-albumin is mentioned as an example. S-nitroso-albumin may be administered for treatment or prevention of respiratory disorders. The compositions may be formulated in a number of different ways. Suitable formulations for parenteral administration include oily injection suspensions, aqueous solutions and aqueous injection suspensions.

Document D10 describes compositions including heme-containing proteins. The invention relates to heme-containing proteins having bound there to non-oxygen gas ligands, for example NO, for in vitro or in vivo use.

Document D1-D10 all show that it is known to associate protein and polypeptides with NO. Many of the documents (D1-D8) also show that it is known to associated sugars and NO. In all the documents it is stated that the active form of

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nitric oxide can be provided by gaseous NO. Further, in D5-D7 and D9-D10 it is explained that nitrosation can be achieved by exposure to NO gas under anaerobic conditions. Consequently, the subject-matter of claims 1-3 and 27 is previously known and therefore lacks novelty.

Documents D1-D10 are all closely related to the present invention. However, documents D3 and D4 are considered to represent the most relevant prior art to the subject-matter of claims 10-11. The invention according to these claims differs from D3 and D5 in that the compound capable of forming a reversible bond or association with NO is specified to a disaccharide or a higher carbohydrate polymer of common monosaccharides or derivates thereof. Due to this difference, the problem to be solved by the present invention may be regarded as creating an alternative composition.

It is natural for a person skilled in the art, trying to solve the above stated problem, to use similar compounds. For the person skilled in the art a disaccharide or a higher carbohydrate polymer of a monosaccharide or a derivate thereof is equivalent to a sugar. It is therefore obvious that it is possible to use disaccharides or higher carbohydrate polymers of the common monosaccharides specified in claim 11. Consequently, the subject-matter of claims 10-11 lacks an inventive step.

According to documents D1 and D2 it is known that it is possible to associate alcohols with NO. The documents describe the use of O-nitrosoalcohol and O-nitroalcohols. Consequently, claim 13 lacks novelty. Further, documents D1 and D2 are considered to represent the most relevant prior art to the subject-matter of claims 14, 16, 19 and 20. The invention according to these claims differs from D1 and D2 in that the compound capable of forming a reversible bond or association with NO is specified to a polymer of alchohol molecules or a mono-, di- or trihydric alcohol. Due to this difference, the problem to be solved by the present invention may be regarded as creating an alternative composition.

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It is natural for a person skilled in the art trying to solve the above stated problem to use similar compounds. It is therefore obvious that it is possible to use the different groups of alcohols specified in claims 14, 16, 18 and 20. Consequently, the subject-matter of claims 14, 16, 18 and 20 lacks an inventive step.

As earlier mentioned document D1-D10 all show that it is known to associate protein and polypeptides with NO. Document D1-D8 also show that it is known to associate N-acetylcysteine and albumin with NO. Consequently, claims 22-25 lack novelty.

Document D3-D8 describe that the compositions can be formulated for parenteral administration. In all the documents emulsions are described as suitable vehicles for parenteral administration. Further, in D3 and D8 a number of different emulsions, suitable for oral and topical administration, are described. The invention according to claims 26, 28 and 35-38 describes different types of formulations and methods for manufactureing compositions. The formulations and methods are well-known for a person skilled in the art of pharmaceutics. Therefore the subject-matter of claims 26, 28 and 35-38 is not considered to involve an inventive step.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawing or on the question whether the claim are fully supported by the description, are made:

The terms "monosaccharide and derivate thereof" used in claim 4 and "disaccharide or derivate thereof" used in claims 10 are vague and unclear.